Anti-Allergens Oral
Therapeutic Class Review (TCR)

May 4, 2020

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FDA-APPROVED INDICATIONS

Drug Name	Manufacturer	Indication(s)
House dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) allergen extract (Odactra®)[1]	ALK-Abelló A/S	Immunotherapy for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts in patients 18 to 65 years of age
Peanut (*Arachis hypogaea*) allergen powder (Palforzia™)[2]	Aimmune Therapeutics	Immunotherapy for the mitigation of allergic reactions to accidental peanut exposure in patients 4 to 17 years of age with a confirmed diagnosis of peanut allergy and in conjunction with a peanut-avoidant diet; it may be continued in patients 18 years of age and older
Short ragweed (*Ambrosia artemisiifolia)* pollen allergen extract (Ragwitek®)[3]	ALK-Abelló A/S / Merck Sharp & Dohme	Immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen in adults 18 years through 65 years of age
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass mixed pollens allergen extract (Oralair®)[4]	Greer	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for any of the 5 grass species contained in this product in persons 5 years through 65 years of age
Timothy grass (*Phleum pratense*) pollen allergen extract (Grastek®)[5]	ALK-Abelló A/S / Merck Sharp & Dohme	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens in persons 5 years through 65 years of age

OVERVIEW

Allergic rhinitis (hay fever), with or without allergic conjunctivitis, affects approximately 8% of adults and 9% of children in the United States (US).[6] Allergen avoidance and medication therapy can provide significant symptom relief, but for many, symptoms remain.[7] For some of these patients, allergen immunotherapy is a reasonable alternative. Subcutaneous immunotherapy (SCIT) has proven to be effective in the management of allergic rhinitis and asthma since the early twentieth century; however, it requires regular injections, typically over a period of 3 to 5 years, and carries the potential of serious systemic allergic reactions in response to the treatment itself. Until 1991, patient-specific allergen vaccines were used.[8] In 1998, the World Allergy Organization (WAO) stated that the cumulative evidence showed sublingual allergen immunotherapy (SLIT) to be an appropriate alternative to SCIT.[9] SLIT gained Food and Drug Administration (FDA) approval for use in the US in 2014 following widespread use in Europe.[10] The 2011 American Academy of Allergy, Asthma, and Immunology (AAAAI) practice parameters on allergen immunotherapy stress the importance of appropriate indications, the absence of significant comorbid conditions, and the patient's ability to comply with allergen immunotherapy.[11] AAAAI states that, in general, most studies demonstrated that SLIT is safe and effective; however, variations in effectiveness have been attributed to the differences in the dose of allergen used. In general, the higher doses of allergen appeared to have a greater impact on symptom improvement. In addition, for the sublingual route, much higher doses are required, compared to the subcutaneous route.

A 2017 practice parameter update on SLIT published by the AAAAI and American College of Allergy, Asthma, and Immunology (ACAAI), recommends that SLIT should only be used for FDA-approved uses and may not be suitable for all patients (e.g., severe, unstable, or uncontrolled asthma, history of severe systemic reaction to any form of immunotherapy).[12] The update states the only FDA-approved SLIT products for allergic rhinitis are Oralair, Grastek and Ragwitek and advises against off-label use of any other SLIT preparations. It also states that SLIT should be used cautiously during pregnancy and breastfeeding, dosing equivalence between products should not be assumed, initial dose of SLIT should occur in the presence of a health care provider, and all patients should receive a prescription for self-injectable epinephrine. Another recommendation is that patients receiving SLIT should have regularly scheduled follow-up care with an allergen specialist to ensure efficacy, safety and adherence with therapy. Specific to dust mite allergy and similar to other allergy treatment measures, AAAAI states that exposure should be minimized via environmental measures (e.g., decrease humidity, proper laundering and allergen-deterrent linens, use of vacuum with high-efficiency particulate air [HEPA] filtration). SLIT was not recommended for patients eligible for immunotherapy; Odactra SLIT was not FDA-approved at the time of guideline development.

The 2015 American Academy of Otolaryngology – Head and Neck Surgery practice guidelines for allergic rhinitis state that clinicians should offer immunotherapy (SLIT or SCIT) for patients who have an inadequate response to pharmacologic therapy, with or without environmental controls, and that both forms of immunotherapy have been proven effective in reducing symptoms.[13] The guidelines add that potential indications for considering immunotherapy include patient preference, adherence, adverse effects of other medications, coexisting allergic asthma, and possible prevention of asthma. The guidelines also mention that there may be long-term cost savings with immunotherapy, and that there is ongoing debate as to which form of immunotherapy is superior. Allergen-specific immunotherapy, including SLIT, may reduce the onset of new sensitizations, and reduce the onset of asthma, although SLIT is not appropriate as monotherapy for the treatment of asthma.[14] According to the World Allergy Organization (WAO) 2013 update of their Sublingual Allergen position paper, improvement in allergic rhinitis persists for 1 to 2 years after discontinuation of 3 years of SLIT with grass pollen extract. A small double-blind, double-dummy study in grass pollen allergic patients showed that the clinical efficacy of SLIT was equivalent to that of SCIT as measured by symptoms and medication use ($p<0.01$). The current challenge is to identify those patients who are most likely to benefit from the administration of SLIT. Patients should have a history of symptoms related to allergen exposure and have a documented positive allergen-specific IgE test. Mono- and polysensitized patients benefit equally well from allergy immunotherapy. WAO suggests that patients in whom pharmacotherapy does not control allergy symptoms or induces undesirable side effects or patients who refuse injections or long-term pharmacotherapy may benefit most from SLIT. WAO advises that SLIT should only be prescribed by physicians with appropriate allergy training and expertise. In general, SLIT appears to be associated with fewer and less severe adverse effects as compared to SCIT.

In 2010, an electronic survey of US homes estimated that 8% of children have food allergies.[15] It is now estimated that peanut allergies, specifically, affect almost 1 million children in the US, and only 20% will outgrow their allergy.[16] Previously, food allergy treatments primarily consisted of avoiding the allergen and promptly treating any accidental exposure.[17] Reaction to peanut exposure varies from mild skin and/or gastrointestinal symptoms to severe angioedema and anaphylaxis. When accidental peanut exposure occurs, antihistamines can manage mild to moderate reactions, but patients must carry an epinephrine auto-injector to treat severe reactions. In January 2020, the FDA approved the first

treatment for oral immunotherapy (OIT), Palforzia.[18] OIT involves feeding an increasing amount of an allergen to a person allergic to that particular allergen. OIT does not cure a food allergy; rather, it induces a level of tolerance that prevents allergic reactions.[19] Though Palforzia is an OIT agent, it has many similarities to the SLIT products in regards to safety, tolerability, and administration issues. Current guidelines on peanut allergy management from key stakeholder groups have not been updated yet to include Palforzia.[20,21,22,23,24,25]

PHARMACOLOGY

SCIT suppresses allergic Th2-mediated inflammation and increases antigen-specific IgG, probably by induction of regulatory T cells (Tregs), immune deviation (Th2 to Th1), and/or apoptosis of effector memory Th2 cells.[26] SLIT induces modest systemic changes consistent with SCIT, but additional local mechanisms in the oral mucosa and/or regional lymph nodes are likely important.

The oral mucosa is a natural site of immune tolerance. Once the allergen is absorbed, the systemic mechanism(s) of SLIT is thought to be similar to SCIT; however, prior to sublingual absorption, the mechanism differs.[27,28,29] Allergen extracts cross the sublingual mucosa, where the allergen molecules are captured by dendritic cells. Within 24 to 48 hours, the dendritic cells migrate to draining cervical lymph nodes and tonsils where they present allergen-derived peptides to native T cells. Within a few days, Treg cells differentiate from naive T cells and exert a suppressive effect on both Th1 and Th2 responses. A production of IL-10 with resulting down-modulation of the immune response has also been reported. In the sublingual mucosa, mast cells, basophils, and eosinophils are less numerous. This characteristic of the oral mucosa is believed to contribute to the lower rates of adverse systemic allergic reactions seen with SLIT.

Subcutaneous and sublingual immunotherapy cause early increases in allergen-specific IgE and blunting of seasonal allergen-specific IgE.[30] In addition, they lead to persistent increases in antigen-specific immunoglobulin G4 (IgG4).

Peanut (*Arachis hypogaea*) allergen powder-dnfp (Palforzia) is a biologic oral immunotherapy consisting of 12% defatted peanut flour with a standardized allergen profile.[31] The exact mechanism of action of Palforzia has not been established; however, it is used in increasing doses to desensitize the individual.

CONTRAINDICATIONS/WARNINGS[32,33,34,35,36]

The SLIT agents in this review are contraindicated in patients with severe, unstable, or uncontrolled asthma, a history of any of the following: severe systemic allergic reaction, severe local reaction after taking any sublingual allergen immunotherapy, or hypersensitivity to any inactive ingredient in the product. Peanut allergen powder-dnfp (Palforzia) is contraindicated in patients with uncontrolled asthma.

Eosinophilic esophagitis has been reported in association with SLIT. If severe or persistent gastro-esophageal symptoms, such as dysphagia or chest pain occur, discontinue SLIT and evaluate for eosinophilic esophagitis. Interrupt SLIT in patients with oral inflammation or oral wounds. Allow for complete healing before restarting therapy. Eosinophilic esophagitis also was reported in clinical trials of Palforzia. All 5 agents in this class are contraindicated in patients with a history of eosinophilic esophagitis.

Boxed warnings for SLIT products include life-threatening systemic and local allergic reactions, including anaphylaxis and laryngopharyngeal edema. Palforzia also carries a boxed warning regarding anaphylaxis. These products may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. These conditions include, but are not limited to, markedly compromised lung function, unstable angina, mast cell disorder, recent myocardial infarction, arrhythmia, and uncontrolled hypertension. Allergen immunotherapies have not been studied in combination; concurrent use may increase the risk for local or systemic adverse reactions. Palforzia should not be initiated in a patient who has experienced severe or life-threatening anaphylaxis within the past 60 days. Patients and caregivers should be able to recognize symptoms of an allergic reaction and anaphylaxis prior to starting therapy. In addition, patients should understand that exercise, hot water exposure, intercurrent illness (e.g., viral infection), fasting, menstruation, inadequate sleep, and use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of allergic reactions. These factors should be considered regarding timing of the dose. The patients should wait to take the dose after strenuous exercise until signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, rapid heart rate) have subsided. The patient should also avoid taking hot showers or baths immediately prior to or within 3 hours after the dose.

Patients receiving SLIT should be observed in a healthcare setting for at least 30 minutes following the initial dose. Auto-injectable epinephrine should be prescribed for all agents within this class, and the patient should be trained on its appropriate use. Agents within this therapeutic class (SLIT and Palforzia) may not be suitable for patients who may be unresponsive to inhaled bronchodilators or epinephrine, such as those receiving beta-blocker, alpha-adrenergic blockers, or ergot alkaloids. In addition, the adverse effects of epinephrine may be potentiated by tricyclic antidepressants, levothyroxine, monoamine oxidase inhibitors (MAOIs), cardiac glycosides, and certain antihistamines.

SLIT has not been studied in people with moderate to severe asthma or those requiring daily medication to treat asthma. In addition, SLIT should be withheld in patients with an acute asthma exacerbation. SLIT has not been studied with concomitant allergen immunotherapy, which may increase the risk of local or systemic side effects. Likewise, Palforzia should be withheld in patients experiencing an acute asthma exacerbation as uncontrolled asthma is a risk factor for serious outcomes. Consider discontinuing peanut allergen powder-dnfp therapy in those with recurrent asthma exacerbations. Palforzia has not been evaluated in patients with severe asthma, persistently uncontrolled asthma, or patients taking long-term systemic corticosteroids.

The manufacturers of Oralair advise that the risks of adverse effects may be increased when treatment is initiated during the grass pollen season.

Odactra should also be withheld in patients with oral inflammation or wounds (e.g., oral lichen planus, mouth ulcers, thrush, oral surgery, dental extraction) to allow for complete healing.

Palforzia should be discontinued in patients who are unable to tolerate up to, and including, the 3 mg dose during the Initial Dose Escalation phase. Dose adjustments should be considered in patients with gastrointestinal adverse reactions (e.g., abdominal pain, vomiting, nausea, oral pruritus, oral paresthesia).

The agents in this review are not indicated for the immediate relief of allergy symptoms.

Risk Evaluation and Mitigation Strategy (REMS) Programs[37]

Due to the risk of anaphylaxis, Palforzia is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Requirements of the REMS program include enrollment of healthcare providers and patients, certification of health care settings (including critical on-site equipment and personnel), certification of pharmacies, and availability of injectable epinephrine at all times.

DRUG INTERACTIONS[38,39,40,41,42]

No clinically relevant drug-drug interactions have been reported.

ADVERSE EFFECTS[43,44,45,46,47]

Local reactions, primarily oral-mucosal in nature, are common with SLIT, most of which are reported to be mild to moderate in severity and subside with continued treatment.[48] No clear risk factors for adverse effects of SLIT have been identified. Tolerability may vary with the type of extract and formulation. SLIT dose has not clearly been correlated to rate or severity of adverse effects. An accelerated induction schedule has not shown to be associated with a greater risk of systemic adverse reactions with SLIT, as with SCIT; however, most adverse effects reported occurred during the induction phase. In clinical studies, most patients with SLIT-related serious adverse reactions had asthma; symptomatic asthma has been identified as a risk factor for SCIT adverse effects. Case reports have suggested that SLIT carries the same risk factors as SCIT, including height of season and history of previous systemic reaction.

Adverse reactions reported in at least 5% of patients in clinical studies with the pollen allergen agents in this review include oral pruritus, throat irritation, ear pruritus, mouth edema, and tongue pruritus.

The most common (≥ 10%) adverse reactions reported with Odactra during clinical trials include throat irritation/tickle, mouth itch, ear itch, uvula or back of the mouth swelling, lip swelling, tongue swelling, nausea, tongue pain, throat swelling, tongue ulcer/sore, stomach pain, mouth ulcer/sore, and taste alteration.

The most common adverse reactions in ≥ 10% of patients (and ≥ 5% greater than placebo) reported with Palforzia included abdominal pain, vomiting, nausea, oral pruritus, oral paresthesia, throat irritation, cough, rhinorrhea, sneezing, throat tightness, wheezing, dyspnea, pruritus, urticaria, anaphylactic reaction, and ear pruritus.

SPECIAL POPULATIONS[49,50,51,52,53]

Pediatrics

Safety and efficacy have been established in patients ≥ 5 years of age for Grastek and Oralair. Safety and efficacy of Ragwitek and Odactra have not been established in pediatric patients. Safety studies of SLIT in young children reported that most adverse reactions were mild or moderate and resolved without treatment.[54]

Safety and efficacy have been established in patients ≥ 4 years of age for Palforzia. Notably, initiation of Palforzia is only approved in patients 4 to 17 years of age; however, Up-dosing and maintenance dosing may be continued in patients 4 years of age and older.

Pregnancy

Data on use in pregnant women is insufficient to inform of a drug-related risk of using Odactra, Oralair and Palforzia during pregnancy. Palforzia does have a pregnancy exposure registry to monitor the outcomes of women exposed to the drug.

Previously assigned Pregnancy Category B, the labeling for Grastek was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and consists of descriptive information rather than an assigned Pregnancy Category. The labeling now states that available human data on the use of Grastek during pregnancy have not established the presence or absence of drug-associated risks.

Likewise, previously assigned Pregnancy Category C, the labeling for Ragwitek was updated in compliance with PLLR. The labeling now states that available human data on the use of Ragwitek during pregnancy have not established the presence or absence of drug-associated risks.

AAAAI and WAO advise that allergen immunotherapy can be continued during pregnancy, but these agents usually are not initiated in a pregnant patient. [55,56]

Geriatrics

Safety and efficacy of Grastek, Oralair, Odactra, Ragwitek, or Palforzia have not been established in patients over 65 years of age.

DOSAGE AND ADMINISTRATION[57,58,59,60,61]

Drug	Indication/Dosages	Package size
House dust mite allergen extract (Odactra)	1 tablet administered sublingually once daily	Sublingual tablet: 3 blister packages of ten 12 standardized quality house dust mite (SQ-HDM) tablets
Peanut (*Arachis hypogaea*) allergen powder (Palforzia)	Initial Dose Escalation: the following doses administered sequentially on a single day, with each separated by 20 to 30 minutes (observation in between doses and for 60 minutes following final dose) – 0.5 mg, 1 mg, 1.5 mg, 3 mg, and 6 mg Up-Dosing: 1 capsule or sachet opened, mixed and administered orally once daily, dose adjusted approximately every 2 weeks Maintenance Dose: one 300mg sachet opened, mixed and administered orally once daily Capsules should be opened, mixed, and administered orally Consult Prescribing Information for detailed dosing and administration	Initial Dose Escalation Kit 1 card with 5 blisters (representing each dose) containing 13 capsules – two 0.5 mg capsules and eleven 1 mg capsules Up-Dosing packaging: ▪ Level 1: forty-five 1 mg capsules ▪ Level 2: ninety 1 mg capsules ▪ Level 3: thirty 1 mg capsules and fifteen 10 mg capsules ▪ Level 4: fifteen 20 mg capsules ▪ Level 5: thirty 20 mg capsules ▪ Level 6: sixty 20 mg capsules ▪ Level 7: fifteen 20 mg and fifteen 100 mg capsules ▪ Level 8: forty-five 20 mg capsules and fifteen 100 mg capsules ▪ Level 9: thirty 100 mg capsules ▪ Level 10: thirty 20 mg and thirty 100 mg capsules ▪ Level 11: fifteen 300 mg sachets Maintenance packaging: thirty 300 mg sachets
Short ragweed pollen allergen extract (Ragwitek)	1 tablet administered sublingually once daily	Sublingual tablet: Amb a 1-Unit 30 and 90 tablet packages
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract (Oralair)	**Adults:** 300 index of reactivity (IR) administered sublingually once daily **Pediatrics:** 100 IR once daily on Day 1; 2 x 100 IR once daily on Day 2; then 300 IR once daily thereafter.	Sublingual tablets: Adult starter pack: three 300 IR tablets Pediatric starter pack: three 100 IR tablets Commercial pack: thirty 300 IR tablets
Timothy grass pollen allergen extract (Grastek)	1 tablet administered sublingually once daily	Sublingual tablet: 2,800 bioequivalent allergy unit (BAU) 30 tablet packages

Patients receiving SLIT or OIT should be prescribed and properly trained on auto-injectable epinephrine for emergency use.

The first dose of SLIT should be administered in a healthcare setting to observe for acute allergic reactions and treated if they occur. Observe patients for at least 30 minutes after administration. SLIT should be administered to children under adult supervision. The sublingual tablets should be removed from the blister with clean dry hands just prior to dosing and placed immediately under the tongue until complete dissolution for at least 1 minute before swallowing. To avoid swallowing, food or beverage should not be taken for 5 minutes following dissolution of the tablet. Hands should be washed after handling the sublingual tablet.

Odactra contains 6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*, composed of a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen. Fish-derived gelatin is an inactive ingredient of Odactra.

Oralair treatment should be initiated at least 16 weeks before the expected onset of the corresponding allergen season, and Grastek and Ragwitek treatment should be initiated at least 12 weeks before. SLIT should be continued throughout the allergen season. For sustained effectiveness for 1 grass pollen season after cessation of treatment, Grastek may be taken daily for 3 consecutive years, including the intervals between the grass pollen seasons. Studies have demonstrated that, during the first 2 years of co-seasonal or continuous dosing, SLIT with grass pollen extract efficacy was more pronounced with the continuous use; however, after 3 years of therapy, both treatment regimens were equally effective in reducing allergy symptoms.[62] Data regarding the safety of starting treatment during the pollen season or restarting treatment after missing a dose of Oralair, Grastek, and Ragwitek are lacking. However, in the clinical trials for Grastek and Ragwitek, treatment interruptions for up to 7 days were allowed.

Palforzia should be used in conjunction with a peanut free diet. Palforzia treatment is administered in 3 sequential phases: Initial Dose Escalation, Up-Dosing, and Maintenance. The product is packaged to provide total capsules/sachets specific for each separate phase. When administered, Palforzia capsules or sachets should be opened with the entire dose mixed well with a few spoonfuls of a refrigerated or room temperature semisolid food, such as applesauce or yogurt. The entire volume should be consumed, and the opened capsule or sachet should be disposed of immediately. In the Initial Dose Escalation phase, all doses are administered on a single day, under the supervision of a healthcare professional in a health care setting enrolled in the REMS. Twenty to 30 minutes should elapse, with observation, between each dose, and patients should be observed for at least 60 minutes following the last dose. Patients who tolerate at least a 3 mg single dose must return to the health care facility to initiate the Up-Dosing phase, if possible, as soon as the next day. If up-dosing cannot be started within 4 days, then the Initial Dose Escalation phase must be repeated. During the Up-Dosing phase, 11 dose levels are given sequentially, each for a duration of 2 weeks. The first dose of each level is administered in a healthcare setting enrolled in the REMS. Patients are observed for at least 60 minutes following the dose. If tolerated, the subsequent doses of that level can be continued at home. Each dose should be consumed with a meal, at approximately the same time each day, preferably in the evening. All doses in each level must be administered sequentially, and patients may advance to the next level every 2 weeks. After all Up-Dosing levels have been completed, patients may continue on a daily 300 mg maintenance dose. Patients missing 3 or more consecutive doses of Palforzia should consult their health care providers, resumption should occur under medical supervision. Prescribers should consider dose modification or discontinuation in patients who do not tolerate the Up-Dosing regimen.

Patients receiving SLIT or OIT should be prescribed and properly trained on auto-injectable epinephrine for emergency use.

CLINICAL TRIALS

Search Strategy

Search strategy included the use of all drugs in this class and the FDA-approved indications. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Limited comparative clinical trials were found.

Rhinoconjunctivitis Total Symptom Score (RTSS) or Rhinoconjunctivitis daily symptom scores (DSS): the total of 6 symptom scores (e.g., sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus, and watery eyes). Each score ranges from 0 to 3 (absent, mild, moderate, severe); the maximum RTSS is 18.[63,64]

Daily Medication Score (DMS) or Daily Rescue Medication Score (RMS): accounts for the use of allowed rescue medication by subjects based on the following scale that assumes increasing effectiveness among medication types: 0 = absent, 1 = antihistamine, 2 = nasal corticosteroid, 3 = oral corticosteroid.

Total Combined Score (TCS): the sum of each daily symptom score (DSS) and daily medication score (DMS) divided by total number of days of the grass pollen season (GPS). The maximum TCS is 54.

Total Nasal Symptom Score (TNSS): the sum of the severity of nasal symptoms on a scale of 0-3, 0 being none and 3 being severe). Measure symptoms include congestion, itching, and sneezing. [65]

Daily Combined Score (CS): the mean of the RTSS and RMS giving equal weight to symptoms and medication use. The CS ranges from 0 to 3.

The FDA considers the point estimate of the improvement of 15% over placebo and an upper limit of the 95% confidence interval (CI) of less than -10% as clinically significant.

House Dust Mite Allergen Extract Odactra[66,67,68,69]

A double-blind, placebo-controlled, randomized clinical trial compared the efficacy of Odactra to placebo in 1,482 adults ages 12 to 85 years old with HDM-induced allergic rhinitis for up to 12 months. The study was conducted in the U.S. and Canada. Allergic rhinitis was confirmed by IgE HDM sensitivity and patients were required to be symptomatic and not taking any symptom-relieving allergy medications at enrollment. Patients with mild to moderate asthma were eligible for enrollment if they required a medium dosed inhaled corticosteroid daily at most. Patients were randomized 1:1 to Odactra or placebo. Other symptom control medications allowed during treatment included oral antihistamines, ocular antihistamines, and nasal corticosteroids. Treatment interruptions up to 7 days were allowed in clinical trials. Efficacy was assessed by self-reported Total Combined Rhinitis Score (TCRS), daily rhinoconjunctivitis symptom scores (DSS; 6 nasal and ocular symptoms rated on a scale of 0 to 3), and daily rhinoconjunctivitis medication scores (DMS; measuring symptom-relieving medication use). The

primary endpoint was the difference between treatment groups in the average TCRS (rhinitis DSS + rhinitis DMS) during the last 8 weeks of treatment. Secondary endpoints included average rhinitis DSS, average rhinitis DMS, and the average Total Combined Score (TCS; rhinoconjunctivitis DSS + rhinoconjunctivitis DMS) during the last 8 weeks of treatment. The mean age was 35 years, 31% had asthma, and 76% were Caucasian. The mean rhinitis DSS at baseline was 7.94 (maximum of 12) in both groups. The mean TCRS during the last 8 weeks of the treatment period was 4.1 for the Odactra group (n=566 included in analysis) and 4.95 for the placebo group (n=620 included in analysis), a treatment difference of -0.8 points (-17.2%; 95% confidence interval [CI], -25 to -9.7). The average rhinitis DSS was 3.55 for the Odactra group and 4.2 for the placebo group, a treatment difference of -0.65 points (-15.5%; 95% CI, -24.4 to -7.3). The average rhinitis DMS was 0.65 for the Odactra group and 0.79 for the placebo group, a treatment difference of -0.14 points (-18.4%; 95% CI, -41 to 4.3 [not significant]). The average TCS was 5.5 for the Odactra group and 6.6 for the placebo group, a treatment difference of -1.1 points (-16.7%; 95% CI, -24.6 to -4).

A similar double-blind, placebo-controlled, randomized clinical trial compared the efficacy of Odactra (n=318) to placebo (n=338) in European adults ages 18 to 66 years old with HDM-induced allergic rhinitis for approximately 12 months. Allergic rhinitis was confirmed by IgE HDM sensitivity and patients were required to be symptomatic and not taking any symptom-relieving allergy medications at enrollment. Patients were randomized to Odactra or placebo. Other symptom control medications allowed during treatment included oral antihistamines, ocular antihistamines, and nasal corticosteroids. Treatment interruptions up to 7 days were allowed in clinical trials. The primary endpoint was the difference between treatment groups in the average TCRS during the last 8 weeks of treatment. Secondary endpoints included average rhinitis DSS, average rhinitis DMS, and the average TCS during the last 8 weeks of treatment. The mean age was 32 years, 98% were Caucasian, and 46% had asthma. The mean rhinitis DSS at baseline was 7.95 in the Odactra group and 8 in the placebo group. The mean TCRS during the last 8 weeks of the treatment period was 5.71 for the Odactra group and 6.81 for the placebo group, a treatment difference of -1.09 points (-16.1%; 95% CI, -25.8 to -5.7). The average rhinitis DSS was 2.84 for the Odactra group and 3.31 for the placebo group, a treatment difference of -0.47 points (-14.1%; 95% CI, -23.8 to -3.9). The average rhinitis DMS was 2.32 for the Odactra group and 2.86 for the placebo group, a treatment difference of -0.54 points (-18.9%; 95% CI, -34.7 to -1.3). The average TCS was 7.91 for the Odactra group and 9.12 for the placebo group, a treatment difference of -1.21 points (-13.2%; 95% CI, -23.7 to -1.5). This trial has been published and included a third group assigned an unapproved strength, house dust mite allergen extract 6 SQ-HDM. While this trial was not completed in the US, it is included in the prescribing information for Odactra.

A third double-blind, placebo-controlled, randomized clinical trial assessed the efficacy of Odactra using an environmental exposure chamber (EEC) in adults 18 to 58 years old (n=83). Allergic rhinitis was confirmed by IgE HDM sensitivity and patients were required to be symptomatic and not taking any symptom-relieving allergy medications at enrollment. Patients were randomized to Odactra or placebo for approximately 24 weeks. The mean age was 27 years, 90% were Caucasian, and 23% had asthma. The primary endpoint was the Total Nasal Symptom Score (TNSS; represents the sum of 4 nasal symptoms: runny nose, stuffy nose, sneezing, and itchy nose). Secondary endpoints included the differences between groups in the average TNSS at weeks 8 and 16 and average Total Symptom Score (TSS; TNSS + 2 ocular symptoms: gritty/itchy eyes and watery eyes) at Week 24. The mean untreated TNSS following HDM EEC challenge was 7.74 (12 points total) in the Odactra group and 7.32 in the placebo group. The mean TNSS at Week 24 was 3.83 in the Odactra group compared to 7.45 in the

placebo group, a difference of -3.62 points (-48.6%; 95% CI, -60.2 to -35.3). The mean TNSS at week 8 was 5.34 in the Odactra group compared to 6.71 in the placebo group, a difference of -1.37 points (-20.4%; 95% CI, -33.3 to -6.8). The mean TNSS at week 16 was 4.82 in the Odactra group compared to 6.9 in the placebo group, a difference of -2.08 points (-30.1%; 95% CI, -42.3 to -16.8). The mean TSS at week 24 was 4.43 in the Odactra group compared to 9.27 in the placebo group, a difference of -4.84 points (-52.2%; 95% CI, -65 to -37). This trial has been published and included a third group assigned an unapproved strength, house dust mite allergen extract 6 SQ-HDM.

Peanut (*Arachis hypogaea*) allergen powder[70,71,72]

The phase 3 PALISADE trial enrolled 555 peanut-allergic patients ages 4 to 55 years (n=499; ages 4 to 17 years). Most patients had a history of peanut anaphylaxis (72%), asthma (53%), or multiple food allergies (66%). Notable exclusion criteria included a history of cardiovascular disease (including uncontrolled or inadequately controlled hypertension), severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days, chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is or is at significant risk of becoming unstable or requiring a change in chronic therapeutic regimen, select gastrointestinal disorders, and mast cell disorders. Eligible patients were randomized 3:1 to peanut (*Arachis hypogaea*) allergen powder-dnfp or matching placebo. The treatment regimen comprised a 1-day, supervised, initial dose escalation phase (from 0.5 mg to 6 mg); an increasing-dose phase, during which the dose was increased gradually every 2 weeks from 3 mg to 300 mg; and a 24-week maintenance phase with a daily dose of 300 mg. Patients were to continue a strict peanut-avoidance diet and to carry injectable epinephrine. At study screening, the median maximum dose of peanut protein tolerated during a food challenge was 10 mg. At the end-of-trial visit, patients were subjected to an exit double-blind, placebo-controlled food challenge (DBPCFC). The primary efficacy endpoint was the proportion of patients 4 to 17 years of age who were considered to have a response to treatment, which was defined as the ability to tolerate a single oral dose of at least 600 mg of peanut protein during the exit food challenge, with no dose-limiting symptoms, as judged by the investigator. After 6 months of maintenance treatment, 67.2% of patients ages 4 to 17 years who received active treatment were able to consume ≥ 600 mg of peanut protein (equivalent to ≥ 2 peanuts) with no reaction or only a mild reaction compared to 4% of patients treated with placebo (63.2% difference; 95% CI, 53 to 73.3; p<0.001). Among patients aged 4 to 17 years, during the treatment period (excluding the exit challenge), 98.7% and 95.2% of patients in the active-drug and placebo groups, respectively, experienced an adverse event, and 4.3% and 0.8%, respectively, were severe events. During the treatment period, 14.2% of patients in the active-drug group and 3.2% in the placebo group had a systemic allergic reaction. In the exit food challenge, 10% of patients in the active-drug group received rescue epinephrine, and the median dose at which it was given was 1,000 mg of peanut protein, compared to 53% of patients in the placebo arm were given epinephrine at a median dose of 100 mg. Efficacy was not shown in participants ≥ 18 years of age.

Short Ragweed Pollen Allergen Extract (Ragwitek)[73]

Two double-blind, placebo-controlled clinical trials in adults ages 18 through 50 years evaluated the efficacy of Ragwitek in the treatment of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis. Approximately 16% of subjects had mild asthma and about 81% were sensitized to other allergens in addition to ragweed at baseline. Patients (n=767) received Ragwitek or placebo for approximately 12 weeks prior to the start of the ragweed pollen season and throughout the ragweed pollen season. Patients were allowed to take medications, including systemic and topical antihistamines

and topical and oral corticosteroids, as needed for symptom relief. Patients self-reported DSS and DMS. The primary endpoint, TCS, was averaged over the peak ragweed pollen season and also averaged over the entire ragweed season. In both studies, relative to placebo, subjects in the Ragwitek group experienced a decrease in TCS during the peak ragweed season (Trial 1: -26% [95% CI, -38.7 to -14.6]; Trial 2: -24% [95% CI, -36.5 to -11.3]) and a decrease in the average TCS from the start of and throughout the entire ragweed pollen season (Trial 1: -26% [95% CI, -37.6 to -13.5]; Trial 2: -27% [95% CI, -38.8 to -14.1]). Decreases relative to placebo were also seen in DSS and DMS in the Ragwitek group.

Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract (Oralair)[74,75]

In a study conducted in US, 473 adults aged 18 through 65 years with a positive skin prick test to Timothy grass pollen extract received Oralair or placebo, starting approximately 4 months prior to the expected onset of the grass-pollen season and continuing for the duration of 1 pollen season. The primary objective was to assess the safety and efficacy of Oralair 300 IR during the grass pollen season. The primary efficacy endpoint parameter was the CS. The Relative Difference, as calculated as the LS mean difference between Oralair and placebo divided by the LS mean of placebo, expressed as a percentage, between Oralair and placebo of the daily CS was -28.2% (95% CI, -43.4 to -13), daily RTSS was -22.9% (95% CI, -38.2 to -7.5), and daily RMS was -46.5% (95% CI, -73.9 to -19.2).

In a similar European study, 311 adults aged 18 to 45 years with a positive skin prick test to 5-grass pollen extract and positive *in vitro* testing for timothy grass-specific serum IgE received 1 of 3 different doses of Oralair or placebo starting approximately 4 months prior to the expected onset of the grass pollen season and continuing for the duration of 1 grass pollen season. The Oralair group was dosed 100 IR on day 1, 200 IR on day 2, and 300 IR on each day thereafter. The relative difference between Oralair and placebo of the daily CS was -29.6% (95% CI, -43.1 to -16.1), daily RTSS was -29.2% (95% CI, -43.4 to -15.1), and daily RMS was -30.1% (95% CI, -49.5 to -10.6).

In a long-term study, a total of 426 adults received Oralair or placebo starting approximately 4 months prior to the grass pollen season and continuing for the entire season. Subjects were treated for 3 consecutive grass pollen seasons (year 1 to year 3). The primary evaluation was the Year 3 pollen period. Participants then entered 2 years of immunotherapy-free follow-up (year 4 and year 5). The results of the analysis of the daily Combined Score for Oralair for treatment Years 1 through 3 were -16.4% (95% CI, -27 to -5.8), -38% (95% CI, -53.4 to -22.6), and -38.3% (95% CI, -54.7 to -22), respectively. Data were insufficient to demonstrate efficacy for 1 or 2 years after discontinuation of immunotherapy.

In a pediatric study, 278 children and adolescents were randomized to receive either placebo or Oralair for 4 months prior to the onset of, and throughout 1 grass pollen season. The Oralair group was dosed 100 IR on day 1, 200 IR on day 2, and 300 IR on each day thereafter. The results of the daily CS, daily RTSS and daily RMS were -30.1% (95% CI, 46.9 to -13.2), -30.6% (95% CI, -47 to -14.1), -29.5% (95% CI, -50.9 to -8), respectively.

Timothy Grass Pollen Allergen Extract (Grastek)[76]

Two 24-week randomized, double-blind, parallel group, clinical trials evaluated the efficacy of Grastek during the first grass pollen season. Subjects were 5 years of age and older with a history of grass pollen-induced rhinitis, with or without conjunctivitis, and sensitivity to Timothy grass pollen as determined by specific testing (IgE). Twenty-five percent of subjects had mild, intermittent asthma and 85% were

sensitized to other allergens in addition to grass pollen. Subjects initiated Grastek (n=752) or placebo (n=749) approximately 12 weeks prior to the pollen season. Symptom-relieving medications were allowed, as needed. Subject self-reported rhinoconjunctivitis daily symptom scores (DSS), measured on a scale of 0 (none) to 3 (severe), and daily medication scores (DMS). The sums of DSS and DMS were combined into the Total Combined Score (TCS) and averaged over the entire grass pollen season. The percent change in TCS during the entire grass pollen season in the Grastek group relative to the placebo group was -23.2% (95% CI, -36 to -13). Similarly, the DSS and DMS were decreased in those treated with Grastek compared to placebo throughout the grass pollen season (DSS, -20% [95% CI, -32 to -10]; DMS, -35% [95% CI, -49.3 to -20.8]), and the TCS was decreased compared to placebo during the peak grass pollen season (-29%; 95% CI, -39 to -15).

The sustained effect of Grastek was evaluated in one 5-year, double-blind study. The study design was similar to that of the 24-week studies. Subjects (n=634) received Grastek or placebo daily for 3 consecutive years and were followed for 2 years without treatment. Subjects treated with Grastek had a decrease in TCS throughout the grass pollen season during the 3 years of active treatment (difference relative to placebo: -34.2 and -40.9% in treatment years 1 and 2, respectively). This effect was sustained during the grass pollen season in the first year after discontinuation of Grastek (difference relative to placebo, -34%), but not in the second year (difference relative to placebo, -27.2%).

SUMMARY

Subcutaneous immunotherapy (SCIT) has proven to be effective in the management of allergic rhinitis and asthma; however, it requires regular injection and is associated with the risk of serious systemic allergic reactions in response to the treatment itself. Sublingual immunotherapy (SLIT) offers several specific advantages over injection immunotherapy in that they can be self-administered by patients or caregivers, do not require injections, and carry a much lower risk of anaphylaxis compared with SCIT. The clinical efficacy of SLIT has been shown to be equivalent to that of SCIT as measured by symptoms and medication use. Improvement in allergic rhinitis has been reported to persist for 1 to 2 years after discontinuation of 3 years of treatment with SLIT with grass pollen extract. Common adverse effects reported are primarily oral-mucosal in nature, most of which are mild to moderate in severity and subside with continued treatment.

FDA approved SLIT products for the management of grass/ragweed pollen allergies include Ragwitek (Short Ragweed Pollen Allergen Extract) for use in adults. Grastek (Timothy Grass Pollen Allergen Extract) and Oralair (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) are approved for use in adults and pediatric patients 5 years of age and older. These agents are dosed sublingually once daily and continuing throughout the allergen season. Oralair is given beginning 16 weeks and Grastek and Ragwitek 12 weeks before the corresponding anticipated allergen season. House dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) sublingual allergen extract (Odactra) offers an alternative treatment to SCIT therapy for patients in whom immunotherapy for house dust mite allergy is appropriate. The first dose of SLIT should be given in a healthcare setting; subsequent doses may be self-administered by the patient or caregiver.

Peanut allergen powder-dnfp (Palforzia) is the first and only FDA-approved oral immunotherapy (OIT) for peanut allergy treatment in patients at least 4 years of age. Palforzia has demonstrated a statistically significant increase in tolerance to peanuts and a reduction in allergic symptoms when used in conjunction with a peanut free diet. Palforzia is not a cure for peanut allergy; desensitization with this

product is intended to continue indefinitely. To date, no adequate trials have been conducted demonstrating sustained tolerance after stopping peanut allergen consumption. All doses administered in the Initial Dose Escalation phase and all dose increases administered in the Up-Dosing phase should be given in a healthcare setting; subsequent doses may be self-administered by the patient or caregiver.

All patients utilizing agents within this class should have injectable epinephrine readily available.

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